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Announcement by the German Federal Environmental Agency

Internal Exposure to Organophosphates of the General Population in Germany and Reference Values for the Organophosphate Metabolites DMP, DMTP and DEP in Urine

Opinion of the Human Biomonitoring Commission of the German Federal Environmental Agency

Contents:

Introduction

After the ban on persistent organochlorinated pesticides, such as DDT, organophosphates are now commonly used as pesticides – in agriculture, in horticulture and in the home. Especially an improper use of these substances may result in high consumer exposures to organophosphates, whether via contaminated food products or via uptake in rooms so treated. In addition, accidental poisoning by organophosphates frequently occurs.

Sufficiently sensitive analysis methods are now available in the field of environmental medicine for determining the general population's exposure to organophosphates, and extensive data exists on the population's actual exposure. The German Human Biomonitoring Commission has therefore defined general-population reference values for certain organophosphate metabolites in urine. The comparison with these values makes it possible to assess individual results from occasional studies and - in other, larger studies - to also follow trends in the exposure of the general population in Germany to organophosphates.

Use and distribution

Organophosphate pesticides are used for pest control and plant protection in agriculture, horticulture and households. The synthesis of organophosphates – organic esters of phosphoric acid, thiophosphoric acid and dithiophosphoric acid – dates back to the 19th century. Systematic synthesis and production for use as insecticides and acaricides started in the 1920s. After the ban on persistent organochlorinated pesticides such as DDT in the

1970s, organophosphates are now widely used: In Germany, over 500 tonnes in agriculture in 1994 [1] and more than 22 tonnes in households in 2000 [1].

Input to the environment and residues on foodstuffs

In the Federal Republic of Germany, maximum permissible quantities of authorised organophosphates in food products range from 0.01-0.05 mg/kg for food products of animal origin and between 0.02 and 3 mg/kg for food products of plant origin [3]. In official food inspections, less than 1% of all samples analysed are found to contain levels exceeding the maximum permissible quantities [4].

Toxicology

Organophosphates inhibit the enzyme acetylcholinesterase (AChE), which catalyses the decomposition of acetylcholine [5]. This is the basis for the insecticidal effect, but also causes toxicity to organisms other than the target organism, including pesticide users. The inhibition of acetylcholinesterase leads to the synaptic cleft becoming overloaded with the neurotransmitter acetylcholine and, consequently, to parasympathicomimetic effects, stimulation of ganglionic transmission and increased impulse transmission to the neuromuscular endplate. The parasympathicomimetic effects can be grouped in two types: muscarinic and nicotinic. Muscarinic effects are: miosis, bradycardia, bronchorrhea and bronchoconstriction, shortness of breath, salivation, diarrhoea and vomiting. Nicotinic effects are: tachycardia, hypertonia, muscular fasciculation, spasms and paralysis, CNS symptoms such as confusion, agitation, delirium, coma and spasms [6]. Improper use in the home may lead to poisoning symptoms [7]. Cases of fatal poisoning from suicidal or accidental exposure of organophosphate applicators have also been described [8].

Neuropsychological effects from chronic exposure to organophosphates, without acute intoxication, have also been discussed [9]. Carcinogenic properties of organophosphates in humans are not known [10]. Studies in various mammalian animal species produced no evidence of an increased mutagenic potential of organophosphates, although these active substances show an increased mutagenic potential in some microbial test systems [10, 11].

Intake of organophosphates

For the general population, intake of organophosphates occurs mainly via residues on or in food; daily organophosphate intake by the general population has been estimated to be 5-10 µg in the USA [12, 13], 7 µg in Finland [14] and 67 µg in Italy [15].

Such an estimate of daily organophosphate intake has not been published for the Federal Republic of Germany to date. However, the results of residue analyses suggest a situation comparable to that in the USA [16], although additional sources – such as triethylphosphate (TEP) in flame retardants present indoors – cannot be ruled out. Foodstuffs are only analysed for the original substances, however; the official analysis methods do not cover any hydrolysis products that may have already been formed on the food plant. Consequently, intake of organophosphates and their metabolites may have been significantly underestimated.

Indoor use is another potential exposure pathway [17, 18]. Of the group of organophosphates, chlorpyrifos in particular was detected in house-dust analyses in Germany, with 95 percentiles below 1 mg/kg, but maximum values of up to 870 mg/kg [19]

and 1,300 mg/kg [20]. Against this background, a potentially significant additional intake has been postulated for, in particular, small children playing on floor [21, 22, 23]. Some studies showed, however, that the children's actual pesticide intake can be assumed to be distinctly smaller [24]. Biomonitoring studies found that these exposure estimates clearly overestimate the actual substance intake [25, 26] and that there was no recognisable link between organophosphate levels in household dust and the metabolite concentrations in the urine of small children who had played on the floor in the respective homes [27].

Resorption and metabolism

Organophosphates are well resorbed after uptake via the oral, dermal, or inhalation route [28, 29] and are rapidly metabolised in the human body [30]. In general, 90% of the compounds are excreted within six to 24 hours of oral uptake [31, 32]. No evidence exists of a longer-term accumulation of organophosphate insecticides in the body [33].

Through hydrolysis and oxidative desulfuration, one or more of six metabolites - dimethyl phosphate (DMP), diethyl phosphate (DEP), dimethyl thiophosphate (DMPT), diethyl thiophosphate (DETP), dimethyl dithiophosphate (DMDTP) and diethyl dithiophosphate (DEDTP) - are formed in the human body from nearly all organophosphate insecticides (Figure 1). These metabolites, therefore, are group-specific and suitable for biological monitoring of exposure to organophosphates [34, 35, 36, 37, 38]. The analysis methods that have been developed in recent years enable the simultaneous determination of all six dialkyl phosphate metabolites, with a detection limit low enough to reliably determine dialkyl phosphate excretion in the normal population [39, 40, 41, 42].

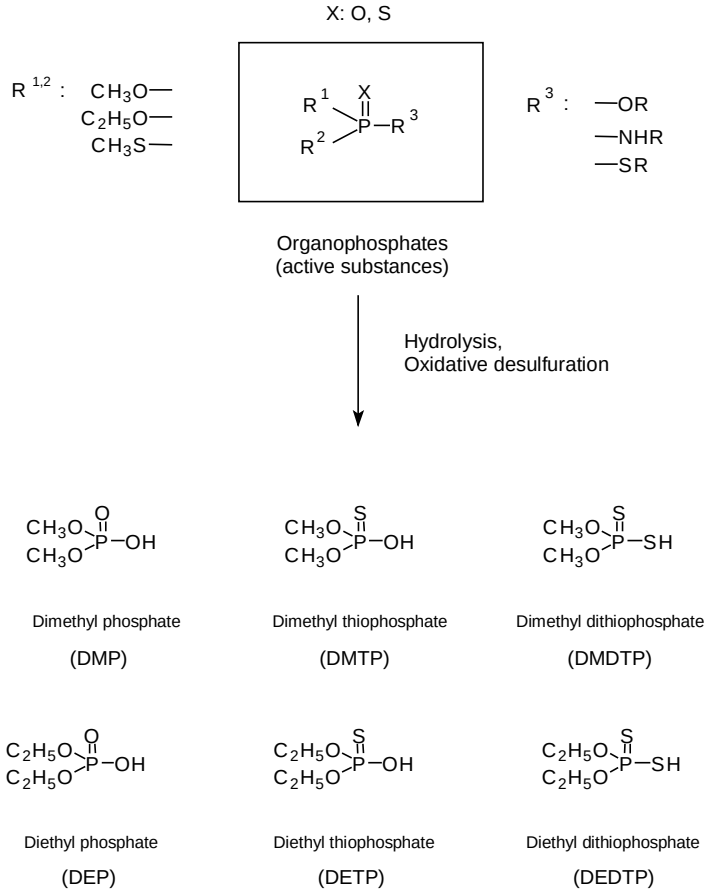

Figure 1: **Group-specific organophosphate metabolites**

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Alternatively, exposure to individual active substances can also be determined by quantifying parameters of higher specificity [43], such as 3,5,6-trichloro-2-pyridonol in urine to monitor uptake of chlorpyrifos [44, 45]. This approach would, however, require several different analysis methods, and many substance-specific parameters have not yet been assessed for their suitability for human biomonitoring. For these reasons, biomonitoring through group-specific parameters was thought to be the adequate approach for routine investigations. Given the biological half-life of a few hours and the relatively rapid elimination, analysis for the metabolites indicates current exposure from a few days prior to analysis; exposures that occurred a week, weeks or months prior cannot be determined with this method.

Analytical determination of organophosphate metabolites in urine

Extraction of alkyl phosphates from urine occurs following addition of an acid, derivatisation, and quantification by means of a combination of gas chromatography and mass selective detection. The details are summarised in Figure 2. The limit of detection of this method is 5 µg/l for DMP and 1 µ/l for the other dialkyl metabolites [41].

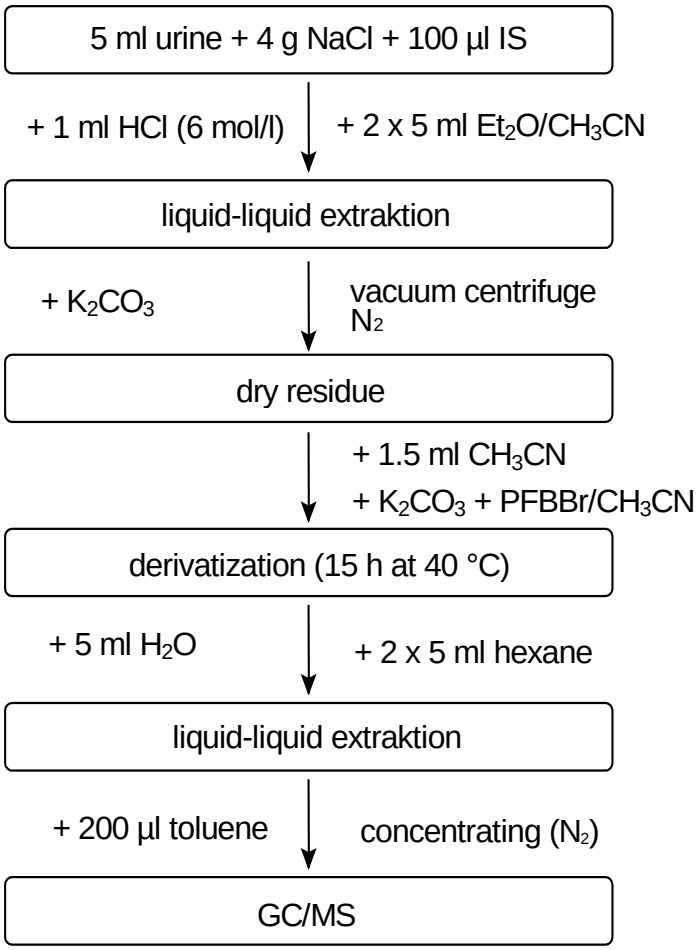

Figure 2: **Sample preparation for determination of organophosphate metabolites (IS, internal standard; Et2O, diethylether; PFBBr pentafluorobenzyl bromide)**

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Internal exposure of the general population

Data on urinary concentrations of organophosphate metabolites in non-occupationally exposed population groups including children are available from various countries. The most important results are listed in Tables 1 and 2.

In initial studies in the USA, Murphy et al. [46] detected DMP, DEP, DMTP and DETP in 6 – 12% of urine samples from the general population. The method used was not sensitive, however (detection limit of 20 µg/l). In a study of children under the age of six, Loewenherz et al. [47] obtained a markedly higher proportion of positive samples. The detection limit here was already lower, at 13 – 15 µg/l.

In a study of 54 non-occupationally exposed adults in Germany which used the analysis method outlined above, DMP, DMTP, DMDTP and DEP could be detected in 90% of the subjects whilst DETP was detectable in 46% and DEDTP in 2% of subjects [16].

Table 1
Percentage of positive analysis results for alkyl phosphates in non-occupationally exposed populations from different countries

Country/ reference	Year of study	LOQ	N	Collective	%>LOQ						
					DMP	DMTP	DMDTP	DEP	DETP	DEDTP	Σ
USA											
[46]	?	20 µg/l	5,976	Adults and children	12	6	< 1	7	6	< 1	
[47]	1995	13-15 µg/l	33	Children <6 years (controls)		28					
[50]	1998	1-7.4 µg/l	110	Children aged 2 – 5 years							70-74
Italy											
[48]	?	<10 nmol/l	124	Adults	87	99	48	82	73	7	
[49]	?		195	Children aged 6-5 years	96	94	33	75	48	12	
Germany											
[16]	Before 1997	1 µg/l (except DMP: 5 µg/l)	54	Adults	96	100	89	94	46	2	
[27]	1998		484	Adults	80	85	32	73	39	2	92
			309	Children <6 years	77	86	33	77	45	3	92
Australia											
[42]	2000	0.02-0.5 µg/l	48	Adults	73	96	48	72	100	2	

LOQ*, limit of quantification;* N*, sample size;* %>LOQ*, percentage of values above LOQ;* ?*, no information available*.

In 1998, the above-mentioned method was used to analyse urine samples of 1,146 children and adults from Frankfurt/Main. There was evidence of a former use of chlorpyrifos in some of the flats where the participants lived. However, the mean and maximum values of chlorpyrifos concentrations in household dust samples were in the range to be expected on the basis of the results of other studies in Germany. The investigations produced no evidence of a link between internal organophosphate exposure and organophosphate (chlorpyrifos) levels in household dust samples from the flats. The proportion of positive urine

samples and average urinary concentrations of metabolites were comparable to the data obtained by Angerer and Hardt in their study [16]. Overall, children exhibited higher urinary concentrations of metabolites than adults [27].

Similar data have been reported from Italy. These studies covered 124 non-occupationally exposed adults and 195 children under the age of six [48, 49]. Sample separation was by gas chromatography, detection by flame photometry after derivatisation with pentafluorobenzyl bromide. The method's limit of detection was approximately 2 µg/l. Here too, the parameters DMP and DMTP exhibited the highest values, and metabolite excretion was higher in children than in adults. Whilst the presence of an own fruit and vegetable garden rarely emerged as a factor influencing internal organophosphate exposure, a slight correlation was found with pest control operations performed in the house or garden in the months preceding the study.

In the spring and autumn of 1998, Lu et al. [50] measured urinary concentrations of DMP, DMTP, DMDTP, DEP, DETP and DEDTP, using gas chromatography and flame photometry, in a total of 110 children between 2 and 5 years of age from 96 households in the Seattle metropolitan area. The method's limits of detection were stated to be 7.4 µg/l for DMP and 6.6 µg/l for DMTP; the detection limit for the other metabolites was 1.1 – 1.2 µg/l. In 99% of the children, one or more of the metabolites was detected. No significant differences were found with respect to the children's age and sex, family income, housing situation, and season.

Oglobline et al. [42] measured urinary concentrations of dialkyl metabolites in 48 adults from Australia non-occupationally exposed to organophosphates. The urine samples were analysed by GC/MS-MS after derivatisation with pentafluorobenzyl bromide. The stated detection limits were: DMP 0.5 µg/l; DMTP and DEP 0.1 µg/l ; DMDTP and DETP 0.04 µg/l; DEDTP 0.02 µg/l. One or more of the dialkyl phosphate metabolites was detected in all samples, and one sample contained all six metabolites in levels above the detection limit. These results also compare well with the data from Germany, Italy and USA (see Tables 1 and 2).

Table 2
Urinary concentrations of organophosphate metabolites in non-occupationally exposed individuals – Adults and children from the general population

Country	Author	Unit	Charac-teristic	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Adults									
Italy	Aprea et al. [48]	µg/g crea	P 50:	9	10	4	4	4	2
			Max:	91	91	21	82	17	10
Germany	Angerer, Hardt [16]	µg/g crea	P 50:	21.2	18.7	1.1	3.5	<LOQ	<LOQ
			P 95:	97.0	145.0	6.0	12.0	7.0	<LOQ
	Heudorf, Angerer [27]	µg/g crea	P 50:	15.5	13.5	<LOQ	2.1	<LOQ	<LOQ
			P 95:	102.5	125.8	13.1	11.6	6.4	<LOQ
Australia	Oglobline et al. [42]	µg/l	P 50 :	13	22	1	3	1	1
			Max:	134	70	141	362	202	1
Children									
Italy	Aprea et al. [49]	nmol/g crea	GM:	116.7	104.3	14.1	33.2	16.0	7.7
			Max:	1471.5	1526.0	754.6	360.1	284.7	140.1
Germany	Heudorf, Angerer [27]	µg/g crea	P 50:	27.4	28.9	<LOQ	4.8	<LOQ	<LOQ
			P 95:	242.0	334.4	24.1	31.4	15.7	<LOQ

crea*, creatinine;* P50, P 90, *percentiles*; Max, *maximum value*; GM, *geometric mean*; LOQ, *limit of quantification*

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Population reference values for organophosphate metabolites in urine

Since there is a need for reference values to characterise the population's exposure to organophosphates, and since the organophosphate excretion data that is available from different studies in Germany so permits and agrees quite well with data from other industrialised countries, the Commission has derived the following reference values from the available data (Table 3):

General population: DMP 135 µg/l
General population: DMTP 160 µg/l
General population: DEP 16 µg/l.

As the volume-related concentrations of organophosphate metabolites show no significant age-dependence, the reference values derived are not age-stratified. For calculation of the reference values (95th percentiles and the associated 95% confidence intervals), the bootstrapping method was used. Reference values were only derived for the organophosphate metabolites DMP, DMTP and DEP as most of the values for these metabolites were above the detection limit (see Table 3). Reference values cannot currently be defined for the organophosphate metabolites DMDTP, DETP and DEDTP, as the majority of the values are below the conventional limit of detection, which is currently given as 1 µg/l (see Table 3).

Table 3:
Urinary concentrations of organophosphate metabolites in the general population in Germany (in µg/l) [27] and 95% confidence intervals for the 95th population percentiles (calculated by the bootstrapping method)

Parameter	N	n>LOQ	Range			P 50	P 90	P 95	KI-PP 95*		
DMP	1,149	903	<5	-	751	16.1	78.5	135.1	115	-	152
DMTP	1,149	992	<1	-	1,668	15.2	92.5	161.8	131	-	193
DMDTP	1,149	382	<1	-	288.8	<1	5.3	11.9	/		/
DEP	1,149	866	<1	-	170.7	2.6	10.7	15.8	14.2	-	17.3
DETP	1,149	501	<1	-	82.8	<1	4.3	7.1	/		/
DEDTP	1,149	26	<1	-	19.3	<1	<1	<1	/		/

N, *sample size*; n>LOQ, *number of values above limit of quantification (LOQ)*; P 50, P 95, *percentiles*; KI-PP 95*, *95% confidence interval for PP 95*, calculated by bootstrapping*; /, *not calculated as doing so would have been pointless*

Measures to be taken guided by reference value

As organophosphate metabolites are substances with short half-lifes, control measurements should be carried out in cases where reference values have been exceeded. Levels above the reference values should be verified several times. If these measurements confirm the initial results a march for potential sources of exposure should be undertaken as reasonably as is achievable. In addition to accidental poisoning, possible sources include indoor contamination following improper pest control operations and food products contaminated by organophosphates.

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